REMARKS

Claims 1-77 were pending. Claims 30, 42, 43, and 71-77 have been cancelled. Claims 1-3, 5, 45-47, 58, and 70 were amended. Claims 78-83 have been added. Therefore, claims 1-29, 31-41, 44-70 and 78-83 are currently pending.

Support for the amendments to claims 1 and 45 can be found, for example, at least in claim 43 as originally filed. Claims 2, 3, 5, 46, 47, 58 and 70 were amended to clarify the invention. Support for new claims 78-80 can be found, for example, in claims 1 and 2 as originally filed. Support for new claims 81-83 can be found, for example, in claims 45 and 46 as originally pending. No new matter has been added.

Copies of references for the February 13, 2002 Information Disclosure Statement, as requested by the Examiner, are filed concurrently herewith.

Provisional Rejection of Claims 1-5, 9, 12-14, 19, 30, 33-51, 54 and 59-70 under the Judicially Created Doctrine of Obviousness-Type Double Patenting

The Examiner provisionally rejected claims 1-5, 9, 12-14, 19, 30, 33-51, 54, and 59-70 under the judicially created doctrine of obviousness-type double patenting over claims 77 and 81 of copending U.S.S.N. 09/823,884. Applicants note that U.S.S.N. 09/823,884 has not yet issued as a patent and, therefore, the double patenting rejection is provisional. Applicants will address the double patenting issue upon a finding of subject matter in the instant application or the copending application that is allowable but for the double patenting rejection.

Rejection of Claims 1-5, 9, 12-14, 19-21, 28, 30, 33-39, 42-51, 54, 55, and 58-70 under 35 U.S.C. § 112, second paragraph

Claims 1-5, 9, 12-14, 19-21, 28, 30, 33-39, 42-51, 54, 55, and 58-70 are rejected under 35 U.S.C. § 112, second paragraph, "as being indefinite for failing to particularly point out and distinctly claim the subject matter which [A]pplicant[s] regard[] as the invention.

In particular, the Examiner found the recitation of the language "cryptosporidium parvum related disorder" in claims 1 and 45 to be unclear. Applicants request clarification of this rejection with respect to claim 1, because claim 1 does not recite the language "cryptosporidium parvum related disorder." With respect to claim 45, Applicants submit that a skilled artisan would be able to use the definition given on page 14, lines 6-8, and would be able to determine disorders which are related to the infection or presence of *Cryptosporidium parvum*. For example, a skilled artisan would be able to

detect the presence or absence of cryptosporidium parvum in a particular subject and then apply the methods of the inventions if necessary.

Applicants respectfully submit that the rejection of claims 2, 3, 46, 47, and 70 under 35 U.S.C. § 112, second paragraph, no longer pertains to the claims as currently amended.

Rejection of Claims 1-5, 9, 12-14, 19, 30, 33-37, and 39-41 under 35 U.S.C. § 102(a)

Claims 1-5, 9, 12-14, 19, 30, 33-37, and 39-41 were rejected under 35 U.S.C. § 102(a) as being unpatentable over Armson *et al.* (*FEMS Microbiology Letters* 178 (1999) 227-233). According to the Examiner, Armson *et al.* "teach the anticryptosporidial activity of doxycycline hydrochloride."

Claim 1 and its dependent claims are directed to methods for controlling *Cryptosporidium parvum* in mammals. The methods include administering to the mammal an effective amount of a tetracycline compound, wherein the tetracycline compound inhibits more than 70% of *Cryptosporidium parvum* at a concentration less than 10 μg/ml.

Armson *et al.* describes the use of a screening assay to determine drugs which may be useful to treat infections of *Cryptosporidium parvum.* As mentioned by the Examiner, one of the compounds tested was doxycycline hydrochloride.

Applicants submit that Armson *et al.* does not anticipate the currently claimed methods. As indicated by Applicants on pages 18 and 19 of the instant specification, doxycycline (e.g., the sixth compound on page 19 in Table 1) inhibits *Cryptosporidium parvum* more than70% only at concentrations above 10 μg/ml.

Therefore, Applicants respectfully request that this rejection of claims 1-5, 9, 12-14, 19, 30, 33-37, and 39-41, under 35 U.S.C. § 102 (a) be withdrawn.

Rejection of Claims 38, 42-51, 54, and 59-70 under 35 U.S.C. § 103 (a)

Claims 38, 42-51, 54, and 59-70 are rejected under 35 U.S.C. § 103 (a) as being unpatentable over Armson *et al.* Claims 42 and 43 have been cancelled, thus rendering their rejection moot.

Claims 38 and 44 are directed to methods for controlling *Cryptosporidium parvum* in mammals. The methods include administering to the mammal an effective amount of a tetracycline compound, wherein the tetracycline compound inhibits more than 70% of *Cryptosporidium parvum* at a concentration less than 10 μg/ml.

Claims 45-51, 54, and 59-70 are directed to methods for treating a *Cryptosporidium parvum* related disorder in a mammal. The method includes

administering to the mammal an effective amount of a tetracycline compound, wherein the tetracycline compound inhibits more than 70% of *Cryptosporidium parvum* at a concentration less than 10 μg/ml.

As described above, Armson *et al.* describes the use of a screening assay to determine drugs which may be useful to treat infections of *Cryptosporidium parvum.* One of the drugs tested by Armson *et al.* was doxycycline.

Armson *et al.* neither teaches nor suggests methods of using tetracycline compounds to control *Cryptosporidium parvum* in mammals with tetracycline compounds which inhibit more than 70% of *Cryptosporidium parvum* at concentrations of less than 10 μg/ml. In contrast, Armson *et al.* describes using doxycycline in an assay. Armson *et al.* does not teach or suggest modifying doxycycline or using other tetracycline compounds as described by Applicants which inhibit more than 70% of *Cryptosporidium parvum* at concentrations less than10 μg/ml.

In addition, Armson *et al.* fails to teach or suggest methods for treating a *Cryptosporidium parvum* related disorder in a mammal, by administering to the mammal an effective amount of a tetracycline compound, wherein the tetracycline compound inhibits more than 70% of *Cryptosporidium parvum* at a concentration less than 10 μg/ml. As described above, Armson *et al.* fails to teach or suggest the use of any tetracycline compounds which inhibit more than 70% of *Cryptosporidium parvum* at concentrations less than 10 μg/ml, as claimed by Applicants.

Therefore, Applicants respectfully request that this rejection of claims 38, 44-51, 54, and 59-70 under 35 U.S.C. § 103(a) be withdrawn.

SUMMARY

Cancellation of and/or amendments to the claims should in no way be construed as an acquiescence to any of the Examiner's objections and/or rejections. The cancellation of the claims is being made solely to expedite prosecution of the above-identified application. Applicants reserve the option to further prosecute the same or similar claims in the present or another patent application. The amendments made to the claims are not related to any issues of patentability.

In view of the above remarks and amendments, it is believed that this application is in condition for allowance. If a telephone conversation with Applicant's Attorney would expedite prosecution of the above-identified application, the Examiner is urged to call Elizabeth A. Hanley, Esq. at (617) 227-7400.

Date: February 28, 2003

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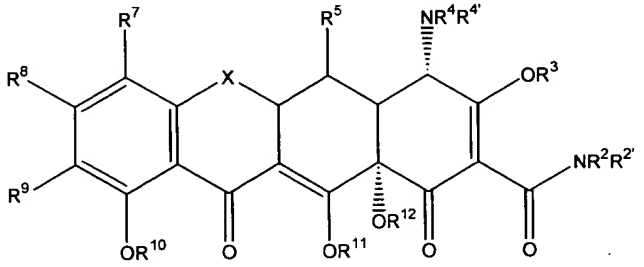
VERSION OF CLAIMS WITH MARKINGS TO SHOW CHANGES MADE

1. [Amended] A method for controlling *Cryptosporidium parvum* in a mammal, comprising administering to said mammal an effective amount of a tetracycline compound, such that *Cryptosporidium parvum* is controlled in said mammal, wherein said tetracycline compound inhibits more than 70% of *Cryptosporidium parvum* at a concentration less than 10 μg/ml.

2. [Amended] The method of claim 1, wherein said tetracycline compound is of formula I:



(I)

wherein:

X is CHC(R^{13}Y'Y), CHR^6, S, NR^6, or O;

R^2, R^4 and $R^{4'}$ are each hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, aryl, heterocyclic, or heteroaromatic ~~or a prodrug moiety~~;

$R^{2'}$, R^3, R^{10}, R^{11} and R^{12} are each hydrogen~~ or a pro-drug moiety~~;

R^5 is hydroxy, hydrogen, thiol, alkanoyl, aroyl, alkaroyl, aryl, heteroaromatic, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

R^6, R^7, R^8 and R^9 are each independently hydrogen, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

R^{13} is hydrogen, hydroxy, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

Y' and Y are each independently hydrogen, halogen, hydroxyl, cyano, sulfhydryl, amino, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

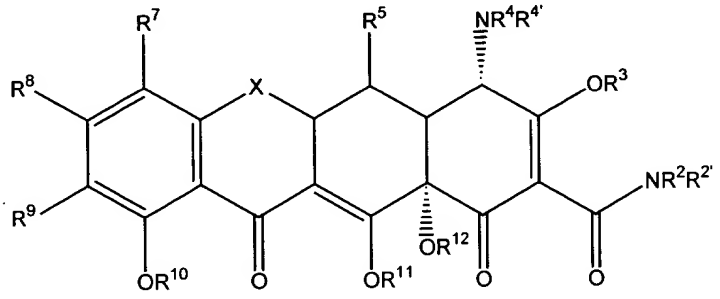
and pharmaceutically acceptable salts thereof.

3. [Amended] The method of claim 2, wherein R^2, $R^{2'}$, R^3, R^{10}, R^{11}, and R^{12} are each hydrogen ~~or a prodrug moiety~~.

5. [Amended] The method of claim 4, ~~5~~ wherein R^4 and $R^{4'}$ are each methyl

45. [Amended] A method for treating a *Cryptosporidium parvum* related disorder in a mammal, comprising administering to said mammal an effective amount of a tetracycline compound such that said mammal is treated for said disorder, wherein said tetracycline compound inhibits more than 70% of *Cryptosporidium parvum* at a concentration less than 10 μg/ml.

46. [Amended] The method of claim 45, wherein said tetracycline compound is of formula I:



(I)

wherein:

X is $CHC(R^{13}Y'Y)$, CHR^6, S, NR^6, or O;

R^2, R^4, and $R^{4'}$ are each independently hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, aryl, heterocyclic or heteroaromatic;

$R^{2'}$, R^3, R^{10}, R^{11} and R^{12} are each hydrogen ~~or a pro-drug moiety~~;

R^5 is hydroxy, hydrogen, thiol, alkanoyl, aroyl, alkaroyl, aryl, heteroaromatic, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or arylalkyl;

R^6, R^7, R^8 and R^9 are each independently hydrogen, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or arylalkyl;

R^{13} is hydrogen, hydroxy, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or arylalkyl;

Y' and Y are each independently hydrogen, halogen, hydroxyl, cyano, sulfhydryl, amino, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or arylalkyl;

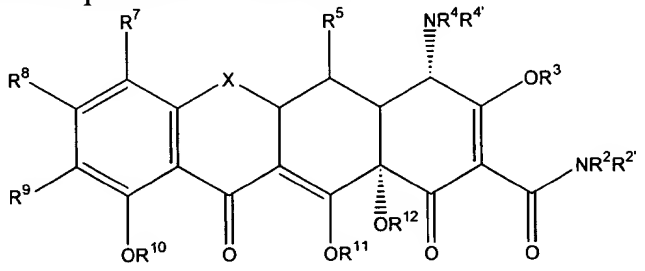
and pharmaceutically acceptable salts thereof.

47. [Amended] The method of claim 46, wherein R^2, $R^{2'}$, R^3, R^{10}, R^{11}, and R^{12} are each hydrogen ~~or a prodrug moiety~~.

58. [Amended] The method of claim 46, wherein said tetracycline compound is selected from the group consisting of 5-propionyl-6-cyclopentylsulfanylmethyl doxycycline; thiatetracycline; 9-cyclopent-1-enyl-doxycycline; 5-propionyl-9-tert-butyl-doxycycline; ~~doxycycline;~~ 9-tert-butyl doxycycline; 9-cyclohex-1-enylethynyl minocycline; and 6-cyclopentylsulfanylmethyl doxycycline.

70. [Amended] The method of claim 46, wherein said supplementary agent is paromomycin ~~or a derivative thereof~~.

78. [New] A method for controlling *Cryptosporidium parvum* in a mammal, comprising administering to said mammal an effective amount of a tetracycline compound, such that *Cryptosporidium parvum* is controlled in said mammal, wherein said tetracycline compound is of formula I:



(I)

wherein:

X is CHC(R^{13}Y'Y), CHR^6, S, NR^6, or O;

R^2, R^4 and $R^{4'}$ are each hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, aryl, heterocyclic, heteroaromatic or a prodrug moiety;

$R^{2'}$, R^3, R^{10}, R^{11} and R^{12} are each hydrogen or a pro-drug moiety;

R^5 is alkanoyl;

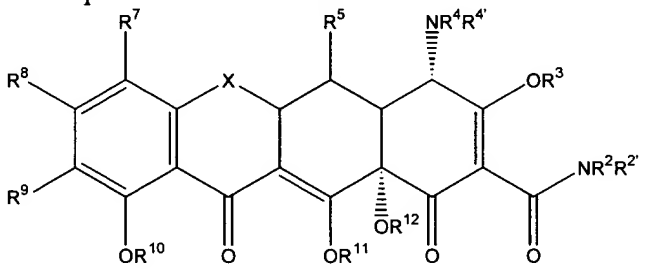
R^6, R^7, R^8 and R^9 are each independently hydrogen, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

R^{13} is hydrogen, hydroxy, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

Y' and Y are each independently hydrogen, halogen, hydroxyl, cyano, sulfhydryl, amino, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

and pharmaceutically acceptable salts thereof.

79. [New] A method for controlling *Cryptosporidium parvum* in a mammal, comprising administering to said mammal an effective amount of a tetracycline compound, such that *Cryptosporidium parvum* is controlled in said mammal, wherein said tetracycline compound is of formula I:



(I)

wherein:

X is $CHC(R^{13}Y'Y)$;

R^2, R^4 and $R^{4'}$ are each hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, aryl, heterocyclic, heteroaromatic or a prodrug moiety;

$R^{2'}$, R^3, R^{10}, R^{11} and R^{12} are each hydrogen or a pro-drug moiety;

R^5 is hydroxy, hydrogen, thiol, alkanoyl, aroyl, alkaroyl, aryl, heteroaromatic, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

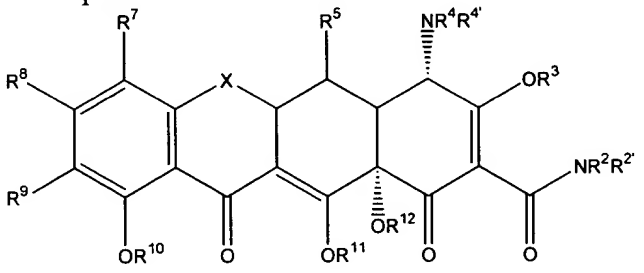
R^6, R^7, R^8 and R^9 are each independently hydrogen, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

R^{13} is hydroxy, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

Y' and Y are each independently hydrogen, halogen, hydroxyl, cyano, sulfhydryl, amino, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

and pharmaceutically acceptable salts thereof.

80. [New] A method for controlling *Cryptosporidium parvum* in a mammal, comprising administering to said mammal an effective amount of a tetracycline compound, such that *Cryptosporidium parvum* is controlled in said mammal, wherein said tetracycline compound is of formula I:



(I)

wherein:

X is CHC(R^{13}Y'Y), CHR^6, S, NR^6, or O;

R^2, R^4 and $R^{4'}$ are each hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, aryl, heterocyclic, heteroaromatic or a prodrug moiety;

$R^{2'}$, R^3, R^{10}, R^{11} and R^{12} are each hydrogen or a pro-drug moiety;

R^5 is hydroxy, hydrogen, thiol, alkanoyl, aroyl, alkaroyl, aryl, heteroaromatic, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

R^6, R^7, and R^8 are each independently hydrogen, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

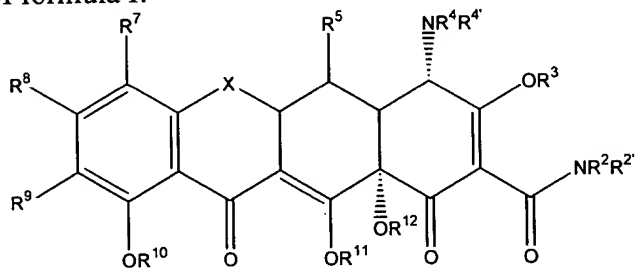
R^9 is hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

R^{13} is hydrogen, hydroxy, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

Y' and Y are each independently hydrogen, halogen, hydroxyl, cyano, sulfhydryl, amino, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

and pharmaceutically acceptable salts thereof.

81. [New] A method for treating a *Cryptosporidium parvum* related disorder in a mammal, comprising administering to said mammal an effective amount of a tetracycline compound such that said mammal is treated for said disorder, wherein said tetracycline compound is of formula I:



(I)

wherein:

X is $CHC(R^{13}Y'Y)$, CHR^6, S, NR^6, or O;

R^2, R^4 and $R^{4'}$ are each hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, aryl, heterocyclic, heteroaromatic or a prodrug moiety;

$R^{2'}$, R^3, R^{10}, R^{11} and R^{12} are each hydrogen or a pro-drug moiety;

R^5 is alkanoyl;

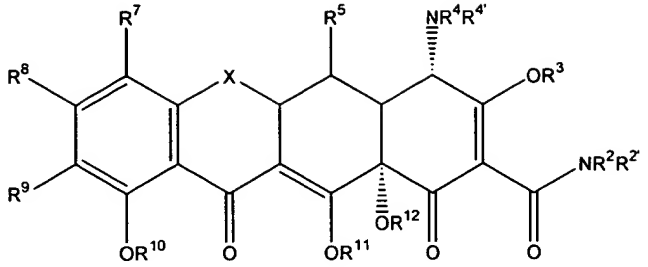
R^6, R^7, R^8 and R^9 are each independently hydrogen, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

R^{13} is hydrogen, hydroxy, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

Y' and Y are each independently hydrogen, halogen, hydroxyl, cyano, sulfhydryl, amino, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

and pharmaceutically acceptable salts thereof.

82. [New] A method for treating a *Cryptosporidium parvum* related disorder in a mammal, comprising administering to said mammal an effective amount of a tetracycline compound such that said mammal is treated for said disorder, wherein said tetracycline compound is of formula I:



(I)

wherein:

X is $CHC(R^{13}Y'Y)$;

R^2, R^4 and $R^{4'}$ are each hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, aryl, heterocyclic, heteroaromatic or a prodrug moiety;

$R^{2'}$, R^3, R^{10}, R^{11} and R^{12} are each hydrogen or a pro-drug moiety;

R^5 is hydroxy, hydrogen, thiol, alkanoyl, aroyl, alkaroyl, aryl, heteroaromatic, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

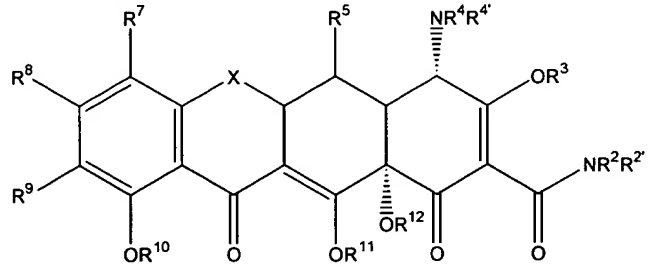
R^6, R^7, R^8 and R^9 are each independently hydrogen, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

R^{13} is hydroxy, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

Y' and Y are each independently hydrogen, halogen, hydroxyl, cyano, sulfhydryl, amino, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

and pharmaceutically acceptable salts thereof.

83. [New] A method for treating a *Cryptosporidium parvum* related disorder in a mammal, comprising administering to said mammal an effective amount of a tetracycline compound such that said mammal is treated for said disorder, wherein said tetracycline compound is of formula I:



(I)

wherein:

X is CHC(R^{13}Y'Y), CHR^6, S, NR^6, or O;

R^2, R^4 and $R^{4'}$ are each hydrogen, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, arylalkyl, aryl, heterocyclic, heteroaromatic or a prodrug moiety;

$R^{2'}$, R^3, R^{10}, R^{11} and R^{12} are each hydrogen or a pro-drug moiety;

R^5 is hydroxy, hydrogen, thiol, alkanoyl, aroyl, alkaroyl, aryl, heteroaromatic, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

R^6, R^7, and R^8 are each independently hydrogen, hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

R^9 is hydroxyl, halogen, thiol, alkyl, alkenyl, alkynyl, aryl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

R^{13} is hydrogen, hydroxy, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

Y' and Y are each independently hydrogen, halogen, hydroxyl, cyano, sulfhydryl, amino, alkyl, alkenyl, alkynyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, or an arylalkyl;

and pharmaceutically acceptable salts thereof.